Potential Antipsychotic Agents. 7.† Synthesis and Antidopaminergic Properties of the Atypical Highly Potent (*S*)-5-Bromo-2,3-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide and Related Compounds. A Comparative Study‡

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(*S*)-5-Bromo-2,3-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide (**6**) and some related compounds, i.e. the *R* isomer **7**, the 3-hydroxy analogue **8**, the desbromo derivative **9**, the monomethoxy compound **10**, and the 2,4-dimethoxy analogue **11**, have been synthesized from the corresponding benzoic acids. The benzamides, lacking *o*-hydroxy groups, were evaluated for their affinity for the [^{3}H]spiperone binding site and for their inhibition of apomorphine-induced behavioral responses in relation to the effect of the corresponding salicylamides. Besides the 2-hydroxy-3-methoxybenzamide **12** and the related 1,4-benzodioxane (**13**) and 2,3-dihydrobenzofuran (**14**), carboxamides were investigated in order to evaluate the stereoelectronic requirements on the 2-methoxy group for the receptor interaction. The study supports the view that the *o*-methoxy group may adopt coplanar, as well as perpendicular orientations, and maintain the intramolecular hydrogen bonding required in the bioactive conformation. The benzamide **6** was found to be equipotent with the analogous highly active salicylamide **3** (FLB 463) both in vitro and in vivo. In addition, **6** displayed a preferential inhibition of the hyperactivity component of the behavioral syndrome, which is regarded to indicate a low tendency to induce extrapyramidal side effects in man at antipsychotically effective doses. The benzamide class of compounds (**6–10**) were found to be somewhat more sensitive to the structural modifications than the salicylamide class, i.e. the *o*-hydroxy-substituted benzamides (**2–5**). The potent and selective benzamide **6** (FLB 457) is highly suitable for investigations of dopamine D-2 mediated responses and, in radiolabeled form, for receptor binding studies in vitro and in vivo.

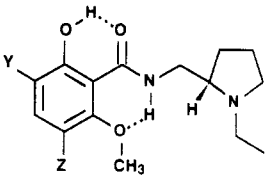
A series of salicylamides, i.e. *o*-hydroxy-substituted benzamides, having selective dopamine D-2 antagonistic properties has been developed in our laboratories.[1-6] Some representative examples are shown in Chart I. The salicylamides **1–3** display an atypical pharmacological profile, i.e. a low cataleptogenic tendency is indicated from animal studies, in combination with a high and stereoselective affinity for the dopamine D-2 receptor.[6,7] The compounds have potential to be effective in the treatment of schizophrenia with a low tendency to induce extrapyramidal side effects (EPS). Thus, raclopride is currently investigated in clinical trials.[8] Furthermore, these properties make the salicylamides suitable for studies on dopaminergic mechanisms and for the development into radioligands.[6,9-11]

The salicylamides are conformationally restricted by one intramolecular hydrogen bond (OH to CO) in addition to the one common for all 2-methoxybenzamides or orthopramides (NH to OMe).[12,13] Modeling studies indicate that a folded or half-folded side chain conformation is present during the receptor interaction.[6,13]

The 5-oxy-6-methoxy-substitution pattern found in **3** gives especially potent dopamine D-2 antagonists both in vitro and in vivo, cf. the compounds **3–5**.[4] The affinity for the dopamine D-2 receptor was only marginally affected by the nature of the 3-substituent (Y). This is in contrast to other types of salicylamides in which the lipophilicity of the 3-substituent is of major importance for their pharmacological properties,[6,14-16] and it underlines the favorable properties inherent to the 5,6-dimethoxysalicylamide system.

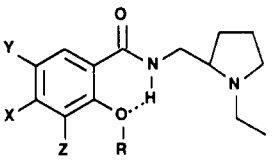
The influence of the *o*-hydroxy group on the activity in this series of substituted benzamides is not clear. The 2,3-dimethoxybenzamide substitution pattern has been used in particular in dopamine antagonists with the piperidinyl type of side chains which require lipophilic nitrogen substituents, e.g. benzyl groups, for their activity (**20**, **21**).[5,17,18] However, other examples such as veralipride,

Chart I



	no.	Y	Z
raclopride	1	Cl	Cl
FLA 797	2	Br	H
FLB 463	3	Br	OCH_3

Chart II



no.	R	Y	X	Z	stereoisomer
6	CH_3	Br	H	OCH_3	S
7	CH_3	Br	H	OCH_3	R
8	CH_3	Br	H	OH	S
9	CH_3	H	H	OCH_3	S
10	CH_3	Br	H	H	S
11	CH_3	Br	OCH_3	H	S
12	H	Br	H	OCH_3	S

N-[(1-allyl-2-pyrrolidinyl)methyl]-2,3-dimethoxy-5-sulfamoylbenzamide, are known.[19,20] In order to further

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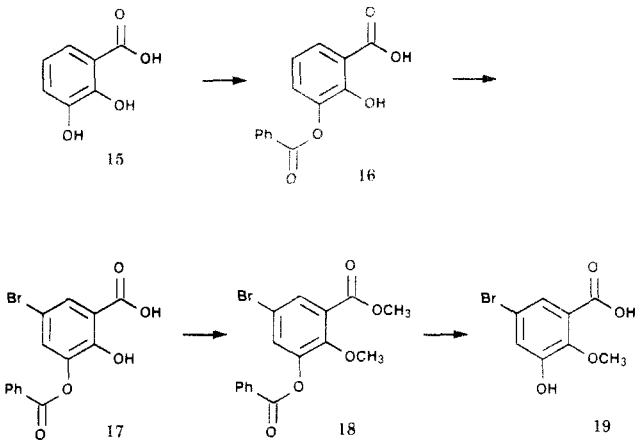
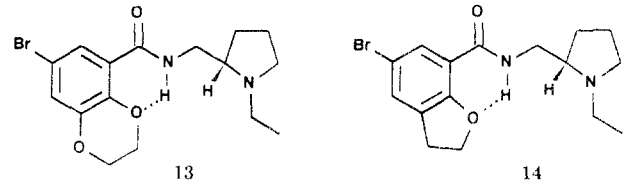
Scheme I



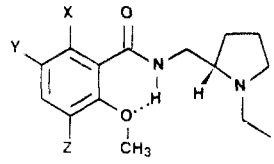
assess the importance of the 2,3-dimethoxybenzamide moiety in compounds with 2-pyrrolidinylmethyl side chains we have synthesized and evaluated a number of benzamides (**6–11**), lacking *o*-hydroxy groups, related to the salicylamides **2–5** (Chart II). The compounds **12–14** were also investigated to learn more about the stereoelectronic requirements on the 2-methoxy group for the receptor interaction.



Chemistry

The benzamides **6–14** were prepared in excellent yields by reacting (*S*)- or (*R*)-2-(aminomethyl)-1-ethylpyrrolidine[21] with the appropriate acyl chloride in dichloromethane at room temperature. The acids used were converted to acyl chlorides by treatment with thionyl chloride in toluene with dimethylformamide as catalyst. The corresponding acids were in most cases made according to known methods. The 5-bromo-3-hydroxy-2-methoxybenzoic acid (**19**) was prepared from **15** in accordance with Scheme I. After protection of the 3-hydroxy group with benzoyl chloride in dimethylformamide the monophenol **16** was brominated para to the hydroxy group in a high yield. Bromo acid **17** was treated with sodium hydride in dimethyl sulfoxide and dimethylated with methyl iodide to give the diester **18**, which was hydrolyzed directly. Purification by chromatography furnished the acid **19** in a moderate overall yield of 11% from **15**.

Table I. Comparison of Salicylamides[4] (X = OH) with the Corresponding Benzamides (X = H) on the Ability To Inhibit [^{3}H]Spiperone Binding (IC_{50}, nM) in Vitro



		X = OH		X = H	
Y	Z	no.	IC_{50}, nM[a]	no.	IC_{50}, nM[a]
Br	H	**2**	12	**10**	46
Br	OCH_3	**3**	1.4	**6**	1.2
Br	OH	**4**	1.9	**8**	10
H	OCH_3	**5**	8.8	**9**	52

[a] Correlation coefficients $r > 0.90$.

Pharmacology

The antidopaminergic effects of the compounds were studied in vitro and in vivo according to previously described procedures.[3,4] The affinity for the dopamine D-2 receptor was assessed by the inhibition of [^{3}H]spiperone binding in rat striatal membranes in vitro.[22] The incubations were done at +37 °C and (+)-butaclamol was used for determination of nonspecific binding. The IC_{50} values were calculated by log-logit regression analysis. The ability of the compounds to block apomorphine-induced behavior in the rat, i.e. hyperactivity and oral stereotypies, were used as estimates for blockade of dopaminergic transmission in limbic and striatal areas, respectively.[3,6] The blockade of the hyperactivity component at lower doses than required for the blockade of stereotypies is regarded as an indication for a lower tendency of the compounds to induce extrapyramidal side effects (EPS) at antipsychotically effective doses in man.[6,7]

Results and Discussion

The potencies to block [^{3}H]spiperone binding to rat striatal homogenate of the compounds **10**, **6**, **8**, and **9**, without *o*-hydroxy groups, are shown in relation to the known corresponding salicylamides **2**, **3**, **4**, and **5**, respectively, in Table I. The 5,6-dimethoxysalicylamide **3** is one order of magnitude more potent than the salicylamide **2** lacking the 5-methoxy group (Z) but equipotent with **4** having a 5-hydroxy group (Z) instead.[4] This shows that the methyl part of the 5-methoxy group is of less importance for the dopamine D-2 inhibiting potency than the oxygen in the same group in this type of salicylamides.

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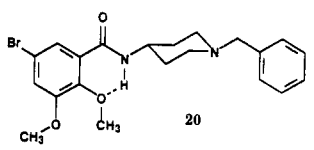
Table II. Antidopaminergic Properties of the Substituted Benzamides **6–14** in Comparison with Some Representative Salicylamides **1–3** and 2,3-Dimethoxybenzamides **20** and **21**

no.	[^{3}H]spiperone binding:[a] IC_{50}, nM	apomorphine antagonism:[b] ED_{50}, μmol/kg ip	
		hyperactivity	stereotypies
1	32	0.13 (0.05–0.23)	1.80 (1.57–2.13)
2	12	0.054 (0.025–0.10)	0.32 (0.29–0.36)
3	1.4	0.009 (0.004–0.017)	0.049 (0.042–0.057)
6	1.2	0.002 (0.0002–0.006)	0.14 (0.12–0.17)
7	145	>20	>20
8	10	1.2 (0.7–1.6)	2.1 (1.7–2.7)
9	52	~10[c]	~10[c]
10	46	3.0 (1.8–4.4)	6.7 (5.6–7.9)
11	44	3.2 (0.8–8.1)	10.7 (9.5–12.1)
12	8210[d]	nt	nt
13	46[e]	3.8 (1.3–7.9)	12.8 (10.9–15.6)
14	7.2	2.0 (0.9–3.5)	4.7 (3.7–6.1)
20	5.0	0.28 (0.24–0.33)	0.24 (0.17–0.29)
21	1.7	0.016 (0.003–0.027)	0.043 (0.036–0.055)

[a] Correlation coefficient $r > 0.90$ unless otherwise indicated. [b] The compounds were injected ip 60 min prior to apomorphine hydrochloride (1 mg/kg sc). The hyperactivity and stereotypies were scored and calculated as described previously.[3,4] The ED_{50} values were calculated by regression analysis with use of Fieller's theorem for estimates of the 95% confidence limits. [c] Interpolated from log dose–response curves. [d] $r = 0.80$. [e] $r = 0.88$.

Thus, the electronic properties of the 5-oxy-6-methoxysalicylamide provide highly active compounds, which is further supported by the moderate drop in activity by the removal of the 3-bromo group from **3** to give **5**.[4]

The benzamide **6** is an equally potent inhibitor of the [^{3}H]spiperone binding as the corresponding salicylamide **3** (Table I). In comparison with the above mentioned salicylamide series, alteration of the Z group leads to larger losses in activity. Thus, the 3-hydroxybenzamide **8** is one order of magnitude less active than **6** and the desbromo (**9**) and the monomethoxy (**10**) benzamides are about 40-fold less active than **6**. This indicates that the salicylamide class can better tolerate and compensate for less optimal Y and Z substituents than the benzamides lacking *o*-hydroxy groups. The 5-bromo-2,3-dimethoxybenzamide **6** is one of the most active non-salicylamides, lacking lipophilic nitrogen substituents, described so far. Tropapride (**21**) is equipotent with **6** in vitro, but the corresponding 1-benzyl-4-piperidinylbenzamide **20** is even less active than **6** (Table II).[5]



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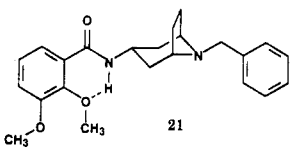

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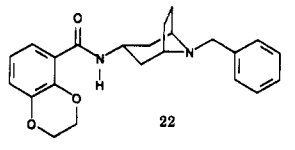

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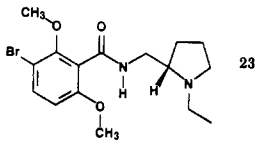

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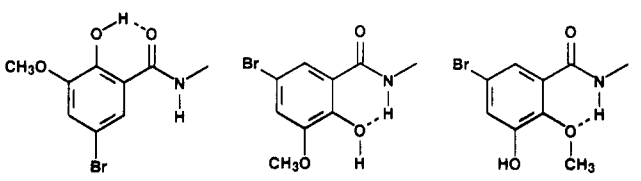
If the 3-methoxy group is moved to the 4-position (**11**) the activity drops and the compound becomes equipotent with the monomethoxy benzamide **10** (Table II). The importance of the 2-methoxy group in the formation of the intramolecular hydrogen bond is demonstrated by the corresponding 2-hydroxy-3-methoxybenzamide **12**, which is virtually devoid of affinity for the [^{3}H]spiperone binding site. Thus, the positive influence of the flanking 3-methoxy group (cf. compounds **6** and **10**) is insufficient to compensate for the omission of the methyl part of the 2-methoxy substituent. The salicylamide **12** may form either rotamer a or b as shown in Figure 1. In rotamer b the methyl group may occupy a region close to that possible in the 1000-fold more active benzamide **8** (c) and hence have a comparable activity (Figure 1). In the investigated



(a) (b) (c)

Figure 1. Two possible hydrogen bonded rotamers (a) and (b) of salicylamide **12** shown in relation to the 1000-fold more active regioisomer **8** (c).

compounds **6–14** the carbonyl groups have ^{13}C NMR chemical shifts in the range of 163.4–165.5 ppm with the exception of **12**, which has a shift of 169.3 ppm. This higher chemical shift is consistent with that in e.g. salicylamide **3** (169.2 ppm) and indicative of a hydrogen bond between the phenol hydrogen and the carbonyl oxygen. Thus, the rotamer a is likely to be the dominating form of **12** in solution (Figure 1), which is in line with its inactivity.[6]

In a recent paper on tropapride (**21**) analogues the high potency associated with the 2,3-dimethoxy system was explained by the reinforcement of the hydrogen bond between the 2-methoxy group and amide group through the electron donating effect of the 3-methoxy group.[18] The antidopaminergic effect (inhibition of apomorphine-induced climbing in mice) was found to follow the chemical shift of the amide hydrogen, which reflects the strength of the intramolecular hydrogen bond. The corresponding 1,4-benzodioxane **22** derivative was considerably (about 1000-fold) less active than tropapride (**21**) in vivo, which was argued to be due to the out of plane orientation of the oxygen electron lone pairs.[18] On the other hand, in the 2,3-dimethoxy system in tropapride the 2-methoxy group is oriented out of plane and accordingly the lone pair is more coplanar with the amide group.[18]

We have previously argued on basis of force field calculations and solid state structures that the 2-methoxy group in the salicylamide series can be either coplanar or perpendicular in compounds with high activity.[4,6,16] It is thus interesting to note that the 1,4-benzodioxane analogue **13** in this series is only about 40-fold less active than **6** in displacing [^{3}H]spiperone (Table II). The ring system is not completely coplanar ($\tau(C_1–C_2–O–C_{ring}) = 160°$; MOPAC V5.0/PM3) in **13** (cf. ref 18), which makes the 2,3-dihydrobenzofuran derivative **14** a more suitable system to test the hypothesis about the role of the orientation of

the oxygen lone pairs for formation of hydrogen bonds. In this derivative we have no marked electronic influence by the 3-substituent as in the case of **6**, **8**, and **13**, and the 2-methoxy group can be regarded as locked into a coplanar conformation ($\tau(C_1-C_2-O-C_{ring})$ = 179°; MOPAC V5.0/PM3) with the oxygen electron lone pairs out of the plane. The 2,3-dihydrobenzofuran **14** displays a high affinity for the [^{3}H]spiperone binding site (Table II), which shows that a coplanar orientation of the 2-methoxy group must provide sufficient hydrogen bonding also in the absence of an electron donating group in the 3-position or the additional intramolecular hydrogen bond found in the salicylamides. In this series of derivatives we did not observe any significant differences in the chemical shift of the amide hydrogen, i.e. 8.30 (**6**), 8.35 (**10**), 8.05 (**13**), and 7.95 (**14**) ppm. The corresponding shifts for **21** and **22** were 8.35 and 7.35 ppm, respectively.[18] The differences between the data in the two series remain unclear, since the conformational effect on the amide hydrogen shift is evident in 2,6-dimethoxybenzamides with established noncoplanarity.[12,23] Thus, the twisted benzamide **23** (remoxipride)[24] displays a chemical shift of 6.30 ppm.

In the series of 5,6-dimethoxysalicylamides (e.g. **3**), relaxation times T_1 and carbon chemical shifts of the methoxy groups showed that the 6-methoxy group adopts a nearly perpendicular orientation and the 5-methoxy group, a more coplanar orientation.[4] Similar studies on **6** showed that the T_1 values of 6.6 s and 2.5 s for the 2-methoxy and 3-methoxy groups, respectively, were practically identical with those of the corresponding groups in **3** (6.5 s and 3.8 s, respectively). This indicates that the dimethoxy groups adopt the same conformations in solution ($CDCl_3$) in the two series. Thus, the present investigation supports our previous notion that the *o*-methoxy group may adopt coplanar as well as perpendicular orientations. However, in the case of 3-methoxy- or 3-hydroxy-substituted 2-methoxybenzamides the energy difference between the two conformers is negligible.[4]

The in vivo activity of the benzamides **6**–**11** and **13**–**14** are shown in relation to the representative salicylamides **1**–**3** in Table II. As can be seen, all salicylamides display a preferential blockade of the hyperactivity component over the stereotypies. Notably, the benzamide **6** is also extremely potent in vivo, i.e. in the same potency range as the analogous salicylamide **3**. The *R* isomer **7** is considerably less active than the *S* isomer **6** in vitro as well as in vivo. The lower potency of **8**–**11** and **13**–**14** in relation to **6** is found also in vivo. These derivatives are only slightly more potent in blocking the apomorphine-induced hyperactivity than the oral stereotypies. However, the most active benzamide **6** shows the desirable preferential inhibition of the hyperactivity component of the behavioral syndrome. Compound **20**, having the same aromatic substitution pattern as **6**, shows no such separation in the behavioral test (Table II). Tropapride (**21**) which is equipotent with **6** in vitro is also very active in the behavioral model but displays a modest functional separation (Table II).

Thus, the 5-bromo-2,3-dimethoxybenzamide **6** (FLB 457) represents one of the most potent dopamine D-2 antagonists of the substituted benzamide class. Its selective action makes it a highly suitable tool for investigations of dopamine D-2 mediated responses and in radiolabeled form for studies of dopamine receptors in vitro and in vivo. Recent studies show that the 5-bromo substituent may be replaced by a wide range of groups while retaining the in vitro affinity.[25]

Experimental Section

Chemistry. Melting points were determined in open capillary tubes on a Mettler FP61 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL FX 200 spectrometer with Me_4Si as internal standard. Mass spectra were obtained on an LKB 2091 instrument. GLCs were run on an SE 30 capillary column, and the amounts determined by a Hewlett-Packard 3390A integrator. Optical rotations were measured on an Optical Activity AA-100 polarimeter. Elemental analyses were performed by Analytische Laboratorium, Elbach, West Germany and are within ±0.4% of the theoretical values.

(−)-(*S*)-5-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,3-dimethoxybenzamide (6). To a solution of 5-bromo-2,3-dimethoxybenzoic acid[5,26] (4.3 g, 0.016 mol) and 0.4 mL of dimethylformamide as catalyst in 45 mL of toluene was added thionyl chloride (4.5 g, 0.038 mol) at room temperature. The mixture was heated to 65 °C for 1 h. After cooling, the solvent was evaporated in vacuo, and the residue consisting of 5-bromo-2,3-dimethoxybenzoyl chloride was dissolved in 25 mL of CH_2Cl_2. A solution of (*S*)-2-(aminomethyl)-1-ethylpyrrolidine[21] (2.6 g, 0.020 mol) in 50 mL of CH_2Cl_2 was added and the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was partitioned between 1 M NaOH and Et_2O. The organic layer was extracted three times with 1 M HCl and the aqueous phase was made alkaline and extracted three times with CH_2Cl_2. Drying and evaporation gave 5.5 g (93%) of pure amide **6** as an oil: ^{1}H NMR ($CDCl_3$) δ 8.30 (br, 1), 7.85 (d, 1, *J* = 2.4 Hz, 6-H), 7.13 (d, 1, *J* = 2.4 Hz, 4-H), 3.89 (s, 6, $(OMe)_2$); ^{13}C NMR ($CDCl_3$) δ 164.0, 153.4, 146.9, 128.2, 125.6, 118.3, 116.9, 62.3, 61.3, 56.4, 53.5, 47.8, 41.1, 28.4, 22.7, 14.0; $[\alpha]^{25}_D$ −59° (*c* 1.15, acetone); MS (EI, 70 eV); *m/z* (rel int) 372/370 (M, 0.07/0.08), 245/243 (0.98/1.04), 98 (100).

The hydrobromide of the title compound was precipitated from acetone/EtOH/Et_2O and recrystallized from EtOAc to give 5.0 g (69%), mp 135–136 °C; $[\alpha]^{25}_D$ −12.5° (*c* 1.04, H_2O). Anal. ($C_{16}H_{23}BrN_2O_3$·HBr): C, H, Br, N.

(+)-(*R*)-5-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,3-dimethoxybenzamide (7) was prepared from 5-bromo-2,3-dimethoxybenzoic acid and (*R*)-2-(aminomethyl)-1-ethylpyrrolidine[11b] according to the above procedure: yield 100% of an oil; $[\alpha]^{22}_D$ +61° (*c* 1.27, acetone).

The hydrobromide salt was prepared and recrystallized from EtOH/Et_2O to give 87%, mp 135–136 °C. Anal. ($C_{16}H_{23}BrN_2O_3$·HBr): C, H, Br, N.

(−)-(*S*)-5-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-3-hydroxy-2-methoxybenzamide (8) was prepared analogously to **6** from 5-bromo-3-hydroxy-2-methoxybenzoic acid (**19**): yield 80% of an oil which solidified; mp 93–95 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1, 6-H), 7.17 (d, 1, 4-H), 3.88 (s, 3, OMe); ^{13}C NMR ($CDCl_3$) δ 165.5, 152.2, 146.2, 127.4, 123.5, 123.3, 116.8, 62.7, 61.0, 53.4, 48.2, 41.4, 28.4, 22.5, 13.3; $[\alpha]^{22}_D$ −59° (*c* 0.34, acetone); MS (EI, 70 eV) *m/z* (rel int) 358/356 (M, 0.03/0.04), 231/229 (0.97/1.08), 98 (100).

(−)-(*S*)-*N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2,3-dimethoxybenzamide (9) was prepared analogously to **6** from 2,3-dimethoxybenzoic acid: yield 100% of an oil; ^{1}H NMR ($CDCl_3$) δ 7.72 (dd, 1, *J* = 1.8 and 7.9 Hz, 6-H), 7.13 (dd, 1, *J* = 7.9 and 7.9 Hz, 5-H), 7.03 (dd, 1, *J* = 1.8 and 7.9 Hz, 4-H), 3.90 (s, 3, OMe), 3.88 (s, 3, OMe); ^{13}C NMR ($CDCl_3$) δ 165.0, 152.3, 147.4, 126.6, 123.9, 122.4, 114.8, 62.1, 60.9, 55.7, 53.2, 47.5, 40.7, 28.0, 22.3, 13.7; $[\alpha]^{22}_D$ −73° (*c* 0.60, acetone); MS (EI, 70 eV) *m/z* (rel int) 292 (M, 0.11), 165 (3.1), 98 (100).

The oxalate salt was prepared by precipitation from acetone/EtOH/Et_2O, mp 104–106 °C. Anal. ($C_{16}H_{24}N_2O_3$·$C_2H_2O_4$): C, H, N, O.

(−)-(*S*)-5-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxybenzamide (10) was prepared analogously to **6** from 5-bromo-2-methoxybenzoic acid: yield 75% of an oil; ^{1}H NMR

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($CDCl_3$) δ 8.35 (br, 1), 8.30 (d, 1, J = 2.6 Hz, 6-H), 7.51 (dd, 1, J = 8.8 and 2.6 Hz, 4-H), 6.85 (d, 1, J = 8.8 Hz, 4-H), 3.94 (s, 3, OMe); ^{13}C NMR ($CDCl_3$) δ 163.8, 156.4, 134.7, 134.5, 123.5, 113.3, 113.1, 61.9, 55.9, 53.4, 47.7, 41.2, 28.2, 22.7, 14.1; $[\alpha]^{25}_D$ −66° (c 0.80, $CHCl_3$).

The oxalate salt was recrystallized from MeOH/Et_2O, mp 135–136 °C. Anal. ($C_{15}H_{21}BrN_2O_2 \cdot C_2H_2O_4$): C, H, Br, N.

(−)-(*S*)-5-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,4-dimethoxybenzamide (11) was prepared analogously to **6** from 5-bromo-2,4-dimethoxybenzoic acid:[5] yield 86% crystalline base (i-Pr_2O); mp 80–81 °C; ^1H NMR ($CDCl_3$) δ 164.0, 158.7, 158.2, 136.2, 115.9, 103.0, 96.1, 62.3, 56.4, 56.1, 53.6, 47.9, 41.4, 28.5, 22.9, 14.2; $[\alpha]^{25}_D$ −63° (c 1.6, acetone). Anal. ($C_{16}H_{23}BrN_2O_3$): C, H, Br, N.

(−)-(*S*)-5-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-3-methoxybenzamide (12) was prepared analogously to **6** from 5-bromo-2-hydroxy-3-methoxybenzoic acid: yield 57% crystalline base (i-Pr_2O); mp 123–125 °C; ^1H NMR ($CDCl_3$) δ 7.38 (d, 1, 6-H), 7.00 (d, 1, 4-H), 3.86 (s, 3, OMe); ^{13}C NMR ($CDCl_3$/MeOD-d_4) δ 169.3, 151.9, 150.2, 121.3, 117.3, 116.4, 108.5, 63.9, 56.0, 53.4, 49.0, 40.7, 27.6, 22.5, 12.7; $[\alpha]^{23}_D$ −38° (c 0.80, acetone). Anal. ($C_{15}H_{21}BrN_2O_3 \cdot H_2O$): C, H, Br, N.

(−)-(*S*)-7-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-1,4-benzodioxan-5-carboxamide (13) was prepared analogously to **6** from 7-bromo-1,4-benzodioxan-5-carboxylic acid: yield 82% of an oil; ^1H NMR ($CDCl_3$) δ 8.05 (br, 1), 7.81 (d, 1, 6-H), 7.10 (d, 1, 4-H); ^{13}C NMR ($CDCl_3$) δ 163.6, 144.3, 141.3, 126.4, 123.8, 122.9, 113.1, 64.6, 63.6, 62.1, 53.6, 48.0, 28.5, 22.9, 14.2; $[\alpha]^{23}_D$ −59° (c 0.80, acetone). Anal. ($C_{16}H_{21}BrN_2O_3$): C, H, N.

(−)-(*S*)-5-Bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,3-dihydrobenzo[*b*]furan-7-carboxamide (14) was prepared analogously to **6** from 5-bromo-2,3-dihydrobenzo[*b*]furan-7-carboxylic acid (**24**): yield 65% crystalline base (i-Pr_2O/hexane); mp 52–54 °C; ^1H NMR ($CDCl_3$) δ 8.02 (d, 1, 6-H), 7.95 (br, 1), 7.36 (d, 1, 4-H); ^{13}C NMR ($CDCl_3$) δ 163.4, 156.8, 131.6, 130.7, 130.3, 117.6, 113.0, 72.7, 62.4, 53.7, 48.5, 42.2, 29.0, 28.8, 23.0, 14.2; $[\alpha]^{25}_D$ −55° (c 0.21, acetone). Anal. ($C_{16}H_{21}BrN_2O_3$): C, H, Br, N, O.

5-Bromo-3-hydroxy-2-methoxybenzoic Acid (19). Benzoyl chloride (23 g, 0.16 mol) was added dropwise to a mixture of 2,3-dihydroxybenzoic acid (12 g, 0.078 mol) and K_2CO_3 (32 g, 0.23 mol) in 150 mL of dimethylformamide. The reaction mixture was heated for 8 h at 80 °C and was then poured into water. The precipitate was recrystallized from acetone/water (3:7) to give 12.2 g (61%) of 3-(benzoyloxy)-2-hydroxybenzoic acid (**16**), mp 194–196 °C.

Bromine (5.8 g, 0.036 mol) was added dropwise to a suspension of the acid **16** (7.7 g, 0.03 mol) and sodium acetate (3.0 g, 0.036 mol) in acetic acid. After stirring for 3 h at 70 °C the mixture was poured into ice–water. The solid was recrystallized from $CHCl_3$/hexane to give 8.1 g (80%) of 3-(benzoyloxy)-5-bromo-2-hydroxybenzoic acid (**17**), mp 172–174 °C. The bromo acid **17** (6.7 g, 0.02 mol) was dissolved in 100 mL of dimethyl sulfoxide and sodium hydride (suspension in mineral oil, 0.05 mol) was added in portions under cooling in an N_2 atmosphere. After the mixture was stirred at room temperature for 2 h, methyl iodide (7.6 g, 0.06 mol) was added and the mixture was heated at 60 °C for 2 h. The mixture was poured into ice–water, extracted with Et_2O, and evaporated. The diester **18** was hydrolyzed by reflux in aqueous KOH, acidified, and extracted with EtOAc.

The crude title compound **19** was purified by chromatography on SiO_2 with EtOAc/HOAc (98:2) and recrystallized from i-Pr_2O/hexane to give 1.0 g (20%) of pure **19**: mp 121–123 °C; ^1H NMR ($CDCl_3$) δ 7.76 (d, 1, 6-H), 7.21 (d, 1, 4-H), 3.96 (s, 3, OMe).

5-Bromo-2,3-dihydrobenzo[*b*]furan-7-carboxylic Acid (24). To a mixture of 2,3-dihydrobenzo[*b*]furancarboxylic acid (5.5 g, 34 mmol) and sodium acetate (5.0 g, 61 mmol) in 50 mL of acetic acid was added a solution of bromine (7.0 g, 44 mmol) in 50 mL of acetic acid. The reaction mixture was heated at 80 °C for 3 h and than poured into ice and filtered. Recrystallization of the precipitate from EtOAc afforded 6.5 g (79%) pure acid **24**: mp 232–234 °C. Anal. ($C_9H_7BrO_3$): C, H, Br, O.

Pharmacology. The assays were performed essentially as described earlier.[3,4,22]

[^{3}H]Spiperone Binding.[22] Rats were killed by decapitation, and the striata were rapidly dissected out on ice. After homogenization in Tris-HCl buffer (0.05 M, pH 7.6) the homogenate was centifuged for 10 min at 48000g, resuspended, and recentrifuged. The final pellet was resuspended in Tris-HCl buffer (0.05 M, pH 7.6) containing 0.1% ascorbic acid and various salts to a final concentration of 5 mg/mL. The incubations were performed at 37 °C for 10 min in plastic trays and terminated by filtration and subsequent washing on glass fiber paper (Whatman GF/B). (+)-Butaclamol (1 μM) was used for the determination of nonspecific binding. The radioactivity of the filters was determined by scintillation spectroscopy. The IC_{50} values were calculated by using log-logit regression analysis.

Blockade of Apomorphine-Induced Behavior.[3,4] Male Sprague-Dawley rats (270–325 g) were used. The behavior was scored 5, 20, 40 and 60 min after injection of apomorphine hydrochloride (1 mg/kg), given subcutaneously into the neck. The scoring was performed as described previously.[4] The test compounds were dissolved in saline or acetic acid and distilled water and injected ip 60 min prior to apomorphine. The ED_{50} values for stereotypies refer to the calculated doses that reduce the scores of apomorphine-induced stereotypies by 50% over the total observation period of 60 min. The ED_{50} values for hyperactivity refer to the calculated doses that reduce the scores of hyperactivity by 50% over the observation period of 60 min of that of the apomorphine control. The ED_{50} values (based on at least six dose levels with 6–8 animals per dose level) for stereotypies and hyperactivity have been calculated by regression analysis with use of Fieller's theorem for calculation of the 95% confidence limit.[4] The ED_{50} value of the response has been defined as the midpoint between the mean of the apomorphine control group and the mean of the saline control group.

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